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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/052,664
Filing Date: January 17, 2002
Appellant(s): CANNON ET AL.

David J. Chang
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/20/2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claim 1 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bork, P., et. al. "Predicting Functions from Protein Sequences-Where are the Bottlenecks" Nature Genetics, Vol 18, pp 313-318

Karp, P.D., Editorial, Bioinformatics, Vol .14, No.9, pp 753-754, 1998

Bork, P., "Sequence and Topology Deriving Biological Knowledge from Genomic Sequences" Current Opinion in Structural Biology, Vol. 8, pp 331-332, 1998

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

A “specific utility” is a utility that is specific to the subject matter claimed, as opposed to a “general utility” that would be applicable to the broad class of the invention. A "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A "well established utility" is a utility that is well known, immediately apparent, or implied by the specifications

disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. A "well established utility" must also be specific and substantial as well as credible.

Based on the record, there is not a "well established utility" for the claimed invention. Applicant has asserted utilities for the specifically claimed invention of claim 1. The invention is directed to an isolated Npt2b polypeptide comprising the amino acid sequence set forth in SEQ ID NO:1.

The specification discloses the human intestinal sodium phosphate co-transporter (Npt2B) polypeptide (SEQ ID NO:1). The specification discloses that a variety of sodium phosphate co-transporters have been identified, and discloses that a variety of disease conditions are associated with disorders in Pi metabolism (page 2). The specification further discloses an extensive list of disorders associated with disorders in Pi metabolism (page 2), and discloses that methods of treating abnormalities in Pi metabolism are varied (page 2). Members of the sodium phosphate co-transporter family are also highly divergent in their effects and ligand specificity. The outcome of the cellular signaling effect varies depending on the specific sodium phosphate co-transporter and the substrate activating said co-transporter. There is no experimental data provided as to the specific functionality of the claimed Npt2B. There is no disclosure of the specific ligands that activate or bind it. Based solely on the homology data to sodium phosphate co-transporters and a general classification into the superfamily of sodium phosphate co-transporters, the specification discloses that the claimed Npt2B is useful for a variety of applications; including research, diagnostic,

and therapeutic agent screening applications and treatment therapies. There is no clear nexus between any treatable diseases/disorders and use of claimed Npt2B. There is no disclosure of the specific activity of the claimed sodium phosphate co-transporter or how to assay for said activity. In light of the specification, the skilled artisan cannot come to any conclusions as to the function of claimed sodium phosphate co-transporter of SEQ ID NO:1 .

The utility of the claimed protein cannot be implicated solely from the homology to the proteins known in the art because the art does not provide a teaching stating that all protein disclosed have the same activity, the same effects, the same ligands and or are involved in the same disease states. In light of the teaching of the specification and art, the skilled artisan cannot come to any conclusions as to the function of the claimed polypeptide. There is no disclosure provided within the instant specification as to what specific function the protein of SEQ ID NO:1 possesses or how to specifically assay for such function. There are no ligands that bind the protein or promoters that activate it. Additionally, there are no target cell types/tissues disclosed and no disease states disclosed that are directly related to protein dysfunction.

The specification fails to disclose what disease is associated with the claimed sodium phosphate co-transporter dysfunction or what drugs affect the specifically claimed sodium phosphate co-transporter function. None of the claims, specification, or prior art disclose the ligand that binds claimed sodium phosphate co-transporter, the activity associated with claimed sodium phosphate co-transporter, how the activity is modulated, or how the modulation or activity is determined using specific assay steps.

The claimed sodium phosphate co-transporter may have utility in the future, when it has been further characterized (e.g. its dysfunction or function correlated with a disease state) and its ligand or functionality determined. The inclusion in the family of sodium phosphate co-transporters does not constitute either a specific and substantial asserted utility or a well established utility for the claimed Npt2Br protein. This is analogous to the reasoning that all proteins/nucleic acid of sodium phosphate co-transporter proteins can be used as markers on a gel.

The specification discloses that the claimed sodium phosphate co-transporters are useful in screening but does not disclose what the claimed sodium phosphate co-transporters specifically regulate or what specific disease the claimed sodium phosphate co-transporter is a target for. What would be the use of using the claimed sodium phosphate co-transporter in a panel for drug screening? It has no known ligand or known function and so is an "orphan". How would one use compounds that interact with said orphan sodium phosphate co-transporter? The specification provides a diverse list of disease states that may be involved in Pi dysfunction. It is unpredictable what ligands would bind to Npt2B and what the result of such binding would be. Further, the functional effects of ligand binding and compound transport may remain uncertain even after extensive experimentation. What is the utility for a ligand having no known function, that binds to an Npt2B of no known function? The ordinary artisan can only speculate as to the utility for the ligand and Npt2B. No utility to orphan Npt2B can be assigned without knowledge of what disease is associated with Npt2B dysfunction or what drugs/ligands affect a Npt2B function. The members of the superfamily of sodium

phosphate co-transporters are highly divergent in their effects and compound specificity. The utility of the claimed sodium phosphate co-transporter cannot be implicated solely from homology to known sodium phosphate co-transporters or their protein domains because the art does not provide a teaching stating that all members of the family of sodium phosphate co-transporters necessarily must have the same effects, have the same ligands or are involved in the same disease states. In fact, the art discloses evidence to the contrary. Appellants have used protein homology to predict the activity of the protein. The utility of the claimed sodium phosphate co-transporter cannot be implicated solely from homology to known sodium phosphate co-transporters or their protein domains because the art does not provide a teaching that all members of family of sodium phosphate co-transporter must have the same effects, the same ligands, and be involved in the same disease states.

Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provides a review disclosing the problems of using homology detection methods to assign function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved" (page 313, column 1, Abstract), b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into a coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function

assignment in sequence databases" (page 313, column 1, third paragraph), c) "In-depth analysis of protein sequences often results in functional predictions not attained in the original studies" (page 313, column 2, last paragraph), d) "---- more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query" (page 315, column 2, last paragraph), and e) pertaining to predictions of protein function, "do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; and even the best hit may have a different function". While "many proteins are multi functional, assignment of a single function, which is still common in genome projects, results in loss of information and outright errors". "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other" (page 316). Karp (Bioinformatics, Vol 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology (page 753, column 2, second paragraph), b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means (page 753, column 2, last paragraph), and c) "research is required

to estimate the error rate of functional annotation by different methods of computational sequence analysis" (page 754, column 2, last paragraph). Bork (Current Opinion in Structural Biology, Vol 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences stating, "structural similarity does not lead to iron-clad functional predictions" (page 331, column 2 last paragraph), " does not necessarily mean a common evolutionary origin" (page 332, column 1, second paragraph), and "Today, what we predict from sequences is at best fragmentary and qualitative" (page 332, column 2, second paragraph). In summary the references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family sodium phosphate co-transporter which has very different ligand specificity and functions.

It can be argued the claimed sodium phosphate co-transporter protein is useful as a tool, as a reagent, and as a molecular target in the diagnosis and treatment of sodium phosphate co-transporter mediated disorders. All members of the sodium phosphate co-transporter protein family have a utility in selectively screening of candidate drugs that target sodium phosphate co-transporters. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case all sodium phosphate co-transporters are in some combination useful in selective screening of candidate drugs that target sodium phosphate co-transporter and in toxicology testing; however, the particulars of screening for candidate drugs that target the claimed sodium phosphate co-transporters, and in toxicology testing are not disclosed in the instant specification. None of the candidate drugs, toxic substances or

the susceptible organ systems are identified. Therefore, this is a utility which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for claimed sodium phosphate co-transporters protein is only useful in the sense that the information that is gained from the assay and is dependent on the effect it has on the protein, and says nothing with regard to each individual sodium phosphate co-transporter family. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants' individual sodium phosphate co-transporter protein is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the instantly claimed method of using sodium phosphate co-transporter protein has no "well-established" use. The artisan is required to perform further experimentation on the claimed sodium phosphate co-transporter protein itself in order to determine to what "use" any information regarding this protein could be put.

With regard to diagnosis of disease, in order for a protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed sodium phosphate co-transporter protein

and a disease or disorder. The presence of the claimed sodium phosphate co-transporter protein in tissue is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed sodium phosphate co-transporter protein and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way as associated with the molecule. There must be some expression pattern that would allow the claimed sodium phosphate co-transporter protein to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed sodium phosphate co-transporter protein is either present only in, e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of claimed sodium phosphate co-transporter protein as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed sodium phosphate co-transporter protein and any disease or disorder and the lack of any correlation between the claimed sodium phosphate co-transporter protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Further, the sodium phosphate co-transporter family to which the polypeptide of SEQ ID NO:1 belongs is a family in which the members have divergent functions based on which tissues the protein is expressed in or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific and utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for drug screening, toxicology testing and diagnosis, is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had

been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use.

Without knowing a biological significance of the claimed sodium phosphate co-transporter protein, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible "real world" manner based on the diversity of biological activities possessed by the sodium phosphate co-transporter family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The assertion that the claimed invention has utility in drug screening, drug development and disease diagnosis, do not meet the standards for a specific, substantial or well-established utility for reasons set forth above. None of the utilities identified have been demonstrated to be specific to the polypeptide of SEQ ID NO:1 . One of ordinary skill in the art must understand how to achieve an immediate and

practical benefit from the claimed species based on the knowledge of the class. However, no practical benefit has been shown for the use of the polypeptide SEQ ID NO:1. Applicant has failed with respect to claimed sodium phosphate co-transporter protein, has not described the family of sodium phosphate co-transporter in enough detail to show, by a preponderance of the evidence, that the polypeptide of SEQ ID NO:1 has any substantial use. The record shows that the family of sodium phosphate co-transporters is diverse, and has such a broad definition, that a "common utility" cannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In *Brenner,* the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

For all the above reasons, the disclosure is insufficient to teach one of skill in the art how to use the invention.

The use of the claimed invention for toxicology testing, drug discovery, and disease diagnosis are not substantial utilities. The question at issue is whether or not the broad general assertion that the claimed sodium phosphate co-transporter protein might be used for some diagnostic application in the absence of a disclosure of which diagnostic application would be considered to be an assertion of a specific, substantial, and credible utility. For reasons set forth above the disclosure satisfies none of the

three criteria *See In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The prior rejection under § 101 followed *Brenner v. Manson*. In that case, the absence of a demonstrated specific utility for the claimed steroid compound was not ameliorated by the existence of a demonstrated general utility for the class. Unlike *Fujikawa v. Wattanasin*, where there were pharmaceutically acceptable in vitro results, here, there is nothing other than relatively low levels of sequence homology to a broad and diverse family of proteins having distinct modes of activity, and no disclosed common mode of action. A rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967.

2. Claim 1 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly

would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed sodium phosphate co-transporter (SEQ ID NO:1) further experimentation is necessary to attribute a utility to the claimed sodium phosphate co-transporter. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

(11) Response to Argument

(A) Utility under 35 USC § 101

Appellants argues the Examiner did not discus the credibility of the utility asserted in the specification.

Appellants' arguments have been fully considered but not found persuasive for the reasons given below:

In the Office action dated 11/20/03 claim 1 is rejected under 35 USC § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Page 3, lines 11-14, of the Office Action dated 11/20/03 states, "A "well established utility" must also be specific and substantial as well as credible. Based on the record, there is not a "well established utility" for the claimed invention". Since the utility is not well established, based on the Examiner's rejection, it is also not credible. Therefore the credibility of the claimed invention has been discussed in the Office Action dated 11/20/03

(B) Standard of Rejection under 35 USC § 101 and Application of Standard of Rejection under 35 USC § 101 for Claim 1.

Appellants' arguments are summarized below:

Appellants submit that the Examiner has not met the burden of presenting a *prima facie* case that the claimed invention lacks patentable utility by providing evidence showing that one of ordinary skill in the art would reasonably doubt the utility asserted in the specification. Appellants state the specification discloses a specific function for the claimed invention, which is a human type II sodium phosphate co-transporter that provides for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells. This is a unique function for Npt2B since no other type II human intestinal sodium phosphate co-transporters have been identified. Based on this unique and specific function of Npt2B, the specification discloses several specific utilities for the claimed invention. One example of a specific utility for the Npt2B polypeptide is its use in various screening assays designed to identify therapeutic agents that modulate Npt2B activity. Another disclosed specific utility for the Npt2B polypeptide is its use as an immunogen to generate antibodies that reduce or inhibit Npt2B activity in a subject. Still another specific utility is the use of the Npt2B protein or protein fragments as therapeutic agents in situations where one wishes to enhance Npt2B activity in a host, e.g. disease conditions associated with hypophosphatemia and in gene therapy to treat disorders associated with Npt2B defects. The Npt2B polypeptide can be used in a screening assay to identify therapeutic agents that modulate Npt2B activity. The claimed polypeptide can be used as an immunogen to

generate antibodies that reduce or inhibit Npt2B activity. In both situations, the claimed Npt2B polypeptide, in its available form at the time of filing, is able to provide benefit to the public by identifying modulatory agents for the treatment of diseases associated with high Npt2B activity, i.e. hyperphosphatemia or with low Npt2B activity, i.e. hypophosphatemia.

Appellants further argue that the general knowledge in the area of Type II sodium phosphate cotransporters, especially the Type IIb intestinal transporter (i.e. Npt2B which is also referred as Napi-IIb) can be ascertained from three references. Hilfiker et al describes the cloning and characterization of mouse Npt2B with a protein sequence, which has 78.8% sequence identity to the amino acid sequence of the claimed invention. Feild et al. and Xu et al. describe the cloning and characterization of human Npt2B/Napii-IIb which show, respectively, 99.7% and 99.9% sequence identity to the Npt2B polypeptide sequence of the claimed invention. The references of Feild et al. and Xu et al. were published three months and ten months after Applicants' priority date. Applicants/Appellants also submit that based on the evidence presented concerning the knowledge possessed by one skilled in the art at the time of filing, the asserted specific and substantial utility for the claimed invention also qualifies as a well-established utility.

Appellants also argue that a recent article by Peerce et al. (Biochem. Biophys. Res. Commun. 301:8-12, 2003) cited in the Declaration of Suryanarayna Sarlkuratri states, "[a] pharmacological method of reducing intestinal phosphate absorption may provide a more palatable approach to reducing serum phosphate and may slow the progression of moderate chronic renal failure to end-stage renal failure. In the proximal

small intestine phosphate absorption occurs by a Na+-dependent mechanism. This statement in Peerce et al. is argued to support and confirm the disclosure in the specification which reads, "[o] f particular interest is the use of the subject methods [of modulating Npt2B activity] to treat hyperphosphatemia resulting from renal insufficiency, e.g. caused by renal disease resulting in at least impaired renal function, and the like."

Appellants also argue that the Declaration under 37 CFR 1.132 by Dr. Suryanarayana Sankuratri, which contains figures and data showing functional characteristics of the claimed Npt2B polypeptide derived by following the procedure disclosed in the specification. The attached Figure 6 in the Declaration is also argued to demonstrate that the asserted utility in the specification of identifying therapeutic agents that modulate Npt2B activity was achieved by the identification of several inhibitors of Npt2B. Applicants/Appellants submit that even if the Examiner was correct in assuming that the Npt2B polypeptide had not yet been expressed in a cell at the time of filing, this does not negate the specific and substantial utility of using Npt2B as an immunogen to generate antibodies that are used to treat specific diseases of phosphate metabolism.

In summary, Applicants argue they have identified and sequenced Npt2B, and set forth several utilities in the specification, including the use in screening assays and the use to generate antibodies. These utilities are argued to be unique to Npt2B, as it is the only sodium-phosphate co-transporter found in the human intestine, and therefore mediates all absorption of phosphate from the diet. Appellants submit that even if the Examiner found that the sodium-phosphate transporter family was diverse, and that one would not expect compounds that affect one transporter to modulate another. Based on

the arguments set forth, Appellants submit that under the Standard of Rejection under 35 USC 101, the Examiner has not met the burden of presenting a *prima facie* case that the claimed invention lacks patentable utility by providing evidence showing that one of ordinary skill in the art would reasonably doubt the utility asserted in the specification.

Appellants' arguments have been fully considered but not found persuasive for the reasons given below:

Appellants states that the specification discloses a specific function for the claimed invention, which is a human type II sodium phosphate co-transporter that provides for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells. This statement is not fully supported by the specification. Page 4, lines 9-10, of the specification state, "A novel human sodium phosphate co-transporter expressed in intestinal cells, as well as polypeptide composition related thereto, are provided". The claimed transporter was not expressed in intestinal cells or any other cells to determine its ion transport properties. The functionality of claimed transporter is based solely on homology to other transporter polypeptides. The specific function of Npt2B cannot be correlated with other known ion transporters since no other type II human intestinal sodium phosphate co-transporters were known in the art at the time of filing instant application. Based on, a) characterization of claimed invention as a novel human sodium phosphate co-transporter due to some homology to other transporter proteins which may vary in ion transport properties, b) lack of expression of claimed transporter in a cell, c) in the absence of characterization of its ion transport properties and d) and assertion that since it is a Pi transporter it must be involved in

some dysfunction involving ion transport, the specification discloses several specific functions and utilities for the claimed Npt2B polypeptide. The references of Karp and Bork, disclosed in subsection 9, above, and discussed in subsection 10, above, disclose the problems of using homology detection methods to assigning function to related members of a family. All transporters are not associated with the same disease states and cannot be used a universal target to treat all the different diseases that may involve ion transport or even Pi or Na transport. Page 2, lines 12-14, of the specification states, "Because of the wide variety of disease conditions characterized by the presence of abnormal Pi metabolism, there is continued interest in the molecular components responsible for Pi metabolism". A variety of disease conditions are associated with disorders in Pi metabolism (see page 1-2 of the specification). The disease conditions include those characterized by the presence of hypophosphatemia, e.g. osteomalacia, hypocalciuria and rickets, and those characterized by the presence of hyperphosphatemia, e.g. hyperparathyroidism, lypocalcemia, vitamin D deficiency, soft tissue or metastatic calcification, and the like. Hyperphosphatemia is a characteristic of renal disease and failure, and is an underlying cause of many of the deleterious symptoms observed with such renal complications. Methods of treating abnormalities in Pi metabolism are varied (see specification page 2). The limited disclosure of a polypeptide, which has been classified as a human type II sodium phosphate co-transporter, cannot be used to establish utility of claimed polypeptide to treat a variety of diseases associated with Pi/Na transport. Further there is no experimental data to

support the statement that the claimed sodium phosphate co-transporter is responsible for absorption and uptake of phosphate in the intestine.

Appellants have previously argued the specification discloses specific diseases associated with the claimed polypeptide are diseases characterized by abnormally high phosphate absorption (various diseases are disclosed), as well as diseases characterized by abnormally low phosphate absorption (various diseases are disclosed). The declaration of Dr. Sankuratri, discloses procedures described, on page 29 of the specification, have been used to show claimed polypeptide transports phosphate ions is responsible for phosphate absorption in the intestine. Further the Declaration by Dr. Sankuratri argues that Npt2B may be used in screening assays to identify inhibitors of transporter function and in turn would be of significant importance in treating diseases characterized by abnormally high phosphate absorption. Also, Dr. Sankuratri compares the biochemical characteristics of Npt2 B with those of Npt2A. The Declaration of Dr. Sankuratri, has been fully considered but not found persuasive. The inclusion in the family of sodium phosphate co-transporter does not constitute either a specific and substantial asserted utility or a well-established utility for the claimed Npt2B polypeptide. This is analogous to the reasoning that all proteins/nucleic acids of sodium phosphate co-transporter proteins can be used as markers on a gel. The specification discloses that the claimed sodium phosphate co-transporter are useful in screening but the specification does not disclose what the claimed sodium phosphate co-transporter specifically regulates or what specific disease the claimed sodium phosphate co-transporter is a target for. The specification provides a diverse list of

disease states that may be involved in Pi dysfunction. A utility to orphan Npt2B cannot be assigned without knowledge of what disease is associated with Npt2B dysfunction or what drugs/ligands affect Npt2B function. The superfamily of sodium phosphate co-transporters is highly divergent in their effects and compound specificity. The utility of the claimed sodium phosphate co-transporter cannot be deduced solely from its homology to known sodium phosphate co-transporters or their protein domains because the art does not provide a teaching that all members of the family of sodium phosphate co-transporters necessarily have the same effects, the same ligands and are involved in the same disease states. In fact, the art discloses evidence to the contrary, as has been set forth supra. The Declaration of Dr. Sankuratri highlights this point. Dr. Sankuratri disclose two transporter proteins, Npt2b and Npt2A, both of which require sodium to transport phosphate, however the uptake kinetics of the two transporters is quite different. Npt2b demonstrated higher affinities for both sodium and phosphate ions than did Npt2A. The two transporters also had opposite responses to pH changes. It is noted that at the time of filing of the instant Patent Application, the claimed polypeptide had not been expressed in a cell to determine its transport properties, or even to specifically show that it transports sodium or phosphate. The sodium dependence of the claimed polypeptide was unknown. In the instant case, post-filing art cannot be used to establish utility because the results of said art were not known at the time of filing of instant application. The unpredictability of assigning a function to the claimed polypeptide based on its relationship to other members of the family is discussed in the prior rejection of record. Even if the claimed polypeptide transports

phosphate, appellants' arguments pertaining to its involvement in disease states characterized by both abnormally high phosphate absorption (various diseases are disclosed), as well as diseases characterized by abnormally low phosphate absorption are not found persuasive. The specific diseases have not been disclosed. The particular involvement in a disease state has not been disclosed. The proposed methods disclosed on page 29 of the specification identified no inhibitors at the time of filing. The claimed polypeptide had not even been expressed in a cell in order to determine its transport properties or even to disclose that it transports sodium and phosphate. It is also not clear how the claimed polypeptide can be simultaneously specific for both disease states that are characterized by abnormally high phosphate absorption and disease states characterized by abnormally low phosphate absorption. Neither the specification nor the prior art discloses an example where interfering with the transport of a specific compound using theclaimed polypeptide, has been associated with the treatment of any specific disease. Many genes expressed in a diseased tissue have nothing whatsoever to do with the disease and are not targets for drug development. For example, actin and histone genes are expressed in disease tissues because they are constitutively expressed in al tissues. These are not suitable targets for drug development since disruption of these genes would kill the patient. Even if the claimed polypeptide transports phosphate, the specification does not disclose any specific and substantial interpretation for any particular disease affected this transport. Would an antagonist be used to treat the disease? Would an agonist be used to treat the disease? What disease would be treated? Further, the person of

ordinary skill in the art would not find substantial the assertion that just because a polypeptide transports phosphate, it automatically is involved in any or all of the diseases claimed by appellants. Given this consideration, the individually claimed sodium phosphate co-transporter protein has no specific, substantial and credible or well-established utility. The skilled artisan is required to perform further experimentation on the claimed sodium phosphate co-transporter protein itself in order to determine to what "use" any information regarding this protein's functionality could be put. The presence of the claimed sodium phosphate co-transporter protein in tissue is not sufficient to establish a utility in the diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed sodium phosphate co-transporter protein and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way as correlative with the molecule. However, in the absence such a disclosed relationship the information disclosed for the claimed polypeptide would only serve as the basis for further research on the polypeptide itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Appellants' argue the claimed sodium phosphate co-transporter protein is useful as a screening tool and that all members of the sodium phosphate co-transporter protein family have utility in the selective screening of candidate drugs that target sodium phosphate co-transporters. However, for a utility to be "well-established" it must

be specific, substantial and credible. All sodium phosphate co-transporters are in some combination useful in the selective screening of candidate drugs that target sodium phosphate co-transporters, the particulars for such screening of candidate drugs that target claimed sodium phosphate co-transporters are not disclosed in the instant specification. Neither the candidate drugs nor the susceptible organ systems are identified. Therefore, this is a utility, which would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed protein for screening compounds that are a target for the claimed sodium phosphate co-transporter protein is only useful in the sense that the information that is gained from the assay is dependent on the effect it has on the protein, and says nothing with regard to the individual sodium phosphate co-transporter family member. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicants' individual sodium phosphate co-transporter protein is affected by a test compound in an assay for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the claimed sodium phosphate co-transporter protein has no "well-established" use. The artisan is required to perform further experimentation on the

claimed sodium phosphate co-transporter protein itself in order to determine to what "use" any information regarding this protein could be put.

Further, polypeptides six amino acids or longer can be used to produce antibodies. However, for a utility to be "well-established" it must be specific, substantial and credible. This is a utility which would apply to virtually every member of a general class of materials. It is also argued that antibodies raised against claimed transporter can be used to bind said transporter or modulate its action. Since the claimed polypeptide has not been shown to have a utility, the antibody that is produced using said polypeptide also has no utility. Further no antibodies are disclosed that specifically bind the claimed transporter polypeptide and modulate its action. Further, because any potential diagnostic utility for the antibody is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the antibody that target the claimed sodium phosphate co-transporter protein is only useful in the sense that it binds the polypeptide and discloses nothing with regard to any function or use in the ion channel. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of polypeptides. Even if the expression of appellants' individual sodium phosphate co-transporter protein is affected by an antibody in a screening assay, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed method of using sodium phosphate co-transporter protein and antibody has no "well-established" use. The artisan is required to perform further experimentation on the

claimed sodium phosphate co-transporter protein and antibody in order to determine to what "use" any information regarding this protein and antibody could be put.

With regard to gene therapy, no specific diseases have been associated with dysfunction of claimed polypeptide. Until a specific disorder is associated with dysfunction of claimed polypeptide its use in gene therapy is not a viable option. Further the claimed polypeptide may not be involved in a any disease state. What would be the use of gene therapy to modulate a gene that is not defective? The use of claimed polypeptide in gene therapy requires further research. The artisan is required to perform further experimentation on the claimed sodium phosphate co-transporter protein and its encoding nucleic acid in order to determine which disease if any would be responsive to gene therapy.

Without knowing a biological significance of the claimed sodium phosphate co-transporter protein, one of ordinary skill in the art would not know how to use the claimed invention. The specification does not disclose a specific and substantial asserted utility or a well-established utility for claimed Npt2B polypeptide in its currently available form, in a credible "real world" manner, based on the diversity of biological activities possessed by the sodium phosphate co-transporter family. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining

whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

For all the above reasons and those presented in the prior Office Action, the disclosure is insufficient to teach one of skill in the art how to use the invention.

A rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967

(C) Enablement under 35 USC § 112, first paragraph.

Appellants' arguments are summarized below:

Appellants argue Examiner's rejection under 35 USC § 1 12, first paragraph was based solely on the utility rejection under 35 USC § 101. From the arguments set forth in Section VIII C1 Appellants submit that the Examiner did not meet the burden of presenting a prima facie case that the claimed invention lacks patentable utility by providing evidence showing that one of ordinary skill in the art would reasonably doubt the utility asserted in the specification. Therefore, appellants argue Claim 1 satisfies the utility requirement of 35 USC § 112, first paragraph . Appellants also assert that Claim 1 satisfies the enablement requirement under 35 USC § 112, first paragraph since the specification would have taught one of ordinary skill in the art how to make and use the invention at the time of filing. The amino acid sequence of the Npt2B polypeptide, as disclosed in Figure 1 and in SEQ ID NO:1, would enable the artisan to generate

antibodies, which can modulate the activity of Npt2B to treat specific diseases of phosphate metabolism.

Appellants' arguments have been fully considered but not found persuasive for the reasons given below:

A rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967)

Claim 1 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed sodium phosphate co-transporter (SEQ ID NO:1), or antibody that binds said co-transporter further experimentation is necessary to attribute a utility to the claimed sodium phosphate co-transporter. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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